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**NAVAL  
POSTGRADUATE  
SCHOOL**

**MONTEREY, CALIFORNIA**

**THESIS**

**A MODEL FOR THE ORDERING AND DISTRIBUTION OF  
THE INFLUENZA VACCINE**

by

James Richard Gurr

June 2006

Thesis Advisor:  
Second Reader:

Walter Owen  
Moshe Kress

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**A MODEL FOR THE ORDERING AND DISTRIBUTION OF THE INFLUENZA  
VACCINE**

James R. Gurr  
Major, United States Army Reserve  
B.S., University of Southern California, 1991  
M.S.E., University of Alabama, Huntsville, 1996

Submitted in partial fulfillment of the  
requirements for the degree of

**MASTER OF SCIENCE IN SYSTEMS ENGINEERING**

from the

**NAVAL POSTGRADUATE SCHOOL  
June 2006**

Author: James Richard Gurr

Approved by: Walter Owen, DPA  
Thesis Advisor

Moshe Kress, Ph.D.  
Second Reader

Dave Olwell, Ph.D.  
Chairman, Department of Systems Engineering

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## **ABSTRACT**

The system for the production and distribution of the United States supply of influenza vaccine has experienced disruptions during past influenza seasons. The process of the identification of elements of the influenza vaccine is different each year and must be researched and identified each year prior to the influenza season. The manufacturing of the vaccine is a complicated process with a lot of potential problems. This thesis identifies the requirements and constraints of the current manufacturing and distribution system including the annual demand and supply. This information is used to create a model based on operational research and operational management theory to develop a systematic approach to distribution of the influenza vaccine in a shortage situation. Two different policies are identified for use in a normal influenza season to determine how many companies are required to provide a sufficient amount of influenza vaccine with the understanding that some of the companies might have manufacturing difficulties. These two policies are the percentage distribution policy and the strict priority distribution policy. The model includes a determination of the number of companies that should be available for influenza vaccine production and the amount of vaccine that should be ordered from each company to minimize the total cost. The majority of the influenza seasons could be covered by purchasing fewer than 108 million doses, as in the percentage distribution policy, making sure that the vaccine dose orders are spread out evenly over four companies and distributed evenly by age group percentage, but could be reduced to as little as 24.5 million total vaccine doses if necessary with minimal cost and loss of life using a strict priority distribution policy.



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## **LIST OF ACRONYMS AND ABBREVIATIONS**

ACIP – Advisory Committee on Immunization Practices

AP – Associated Press

AMDA - American Medical Directors Association

CBC – Canadian Broadcasting Corporation

CBO – Congressional Budget Office

CIDRAP – Center for Infectious Disease Research And Policy, University of Minnesota

CCIAP – Canadian Coalition for Immunization Awareness and Promotion

CDC – Center for Disease Control

FDA – Federal Drug Administration

HA – Hemagglutinin

LAIV – Live Attenuated Inactive Vaccine

MDV – Master Donor Virus

MMWR – Mortality and Morbidity Weekly Review

NA – Neuraminidase

NFID – National Foundation of Infectious Disease

USD HHS – United States Department of Health and Human Services

VRBPAC – Vaccines and Related Biological Products Advisory Committee

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# I. INTRODUCTION

## A. BACKGROUND

Each year there is an estimated 36,000 deaths and 200,000 hospitalizations (CDC, July 2005) in the United States due to health problems stemming from the influenza virus. Ninety percent of deaths related to underlying respiratory and circulatory illnesses associated with the influenza virus occur among adults older than 65 years of age (THOMPSON, 2003). An untreated flu pandemic could cause widespread sickness and death in the United States among all age groups if the country is not ready for the possibility. However, during a normal influenza season panic can still occur if there is a shortage of influenza vaccine for distribution. In 2004, a limited supply of the Flu Vaccine developed a panic in the United States. Mostly the elderly were affected by waiting in long lines for the opportunity to receive the influenza vaccine. An elderly woman actually died in line waiting with her husband (AP, 2004). Chiron Corporation, one of the two companies licensed to provide the flu vaccine in the United States at the time, had to withdraw 48 million doses of the inactivated vaccine (Fluvirin®) that the company expected to deliver in 2004. That turned out to be half of the 100 million doses that were expected to cover the United States population (LA MONTAGNE, 2004). Sanofi-Aventis, another authorized United States vaccine manufacturer, was able to provide an additional 1.1 million doses of live intranasal vaccine (Flumist) to cover the shortage (TREANOR, 2004). Luckily, the flu season ended up as being mild and the limited supply of the vaccine did not appear to cause additional deaths (YEE, 2005). However, what steps can be taken to minimize the risks of this type of situation?

The range of annual demand for flu vaccine is usually 75 to 100 million doses (CDC, June 2005). The type of flu season, from mild to bad, will alter the number of shots demanded by the public. The demand, therefore, can be said to be unknown from year to year as can the supply. A discussion of the problems identified with the influenza vaccine supply and demand estimates are detailed in this thesis. The average amount of influenza vaccine ordered, the overall supply chain and the number of United States

suppliers were used in the development of a model to determine how many companies there should be and the number requested from each company to provide a sufficient supply.

## **B. PURPOSE**

The purpose of this thesis is to determine the number of doses of influenza vaccine required to order from a determined number of manufacturers to prepare for influenza vaccine shortages in the future like the shortage in the 2004 flu season. The thesis also looks at how to use the vaccine on hand when a shortage occurs to minimize overall cost. The supply of influenza vaccine is problematic due to the process of matching the influenza vaccine components with the expected viruses year to year. Two policies are discussed in this thesis to distribute the influenza vaccine: a strict priority distribution policy and a percentage distribution policy.

A systems engineering approach to the production of the vaccine and the supply and demand chain is utilized to develop a model to minimize cost by spreading the vaccine production over several companies and focusing the distribution of the vaccine produced to specific target age groups. A detailed review of the current system, the manufacturing and distribution processes, and the stakeholders in the system was accomplished in Chapter I and Chapter II. The system was decomposed into separate parts to be analyzed. (HATLEY, 2000) A look at other models that were developed was also accomplished to try to understand the current system. Starting with the existing architecture and current system stakeholder's requirements and distribution process a review of the distribution of vaccination purchases and the distribution policies were analyzed to try to develop the policy for the desired optimized outcome, the minimization of cost in a shortage situation. (FORSBERG, 2000) The process is simply to deliver the required vaccine to the customer when required to avoid death. This becomes difficult when there is a limited supply of vaccine. Understanding the production difficulties, the supply process of the vaccine to the distributors and then to the customers, and the customer demand are all important aspects of the system. These were reviewed to determine a better way of manufacturing and distributing the vaccine. This model is theoretical and would be difficult to check without the backing of the CDC and all other

stakeholders. For now, we can only complete the system engineering process by utilizing the Vaccine Model that was developed and determine the best number of companies and the amount to order from each, and the calculated results of distributing the vaccine to customers in the two policies developed.

### **C. RESEARCH QUESTIONS**

Viewing the recent shortage of the Flu vaccine and the effect on the people in the United States led to the questions below. What were the main reasons for the shortage of Flu Vaccine during the 2004-2005 influenza season? What factors affect the demand and supply of the influenza vaccine annually? What research has already been accomplished or is ongoing related to problems associated with the influenza vaccine supply and demand estimates and the overall supply chain? What is the number of United States suppliers currently for Influenza Vaccine and how was that number determined? Is it feasible for the United States government to implement a strategy of government supply commitments to increase the amount of suppliers and reduce risk of undersupply? Can a reasonable solution to this problem be found by modeling the demand as uncertain and the supply as uncertain which develops an adequate Influenza Vaccine required to cover the demand? The ultimate question to be answered is how many influenza shots should be ordered from a set number of companies to minimize the effect of a shortage, to cover as many customers as possible, and to minimize the overall cost of vaccination orders and lost earnings from all deaths. The number of vaccines ordered should minimize cost while covering the demand.

### **D. BENEFITS OF THESIS**

This thesis reviews the influenza vaccine production process and distribution and related problems associated with the vaccine production, new production technologies, and companies that have licenses in the United States to provide the influenza vaccine and those companies that are in the process of acquiring the license to do so. The more companies that have a license to produce the vaccine in the United States the easier it will be to produce and distribute the vaccine and avoid a shortage. The question to be answered is how many influenza shots should be ordered to avoid a shortage to cover as many customers as possible, and to minimize the overall cost of vaccination orders and lost earnings from all deaths. The number of companies used and vaccines ordered

should minimize cost while covering the demand. The death rates of specified age groups in the United States are used to develop a model to determine how many companies are needed to spread the vaccine purchase to ensure an adequate supply, how much vaccine should be ordered from each separate company, and which age groups should get the vaccine in order. The cost of the vaccine doses purchased and the cost of each death are minimized to minimize overall cost to the United States.

The influenza vaccine is a long lead time product. The current vaccine production takes several months so manufacturers must predict the demand and decide how much of the vaccine to produce. If a sufficient number of influenza vaccines are not produced and available during a normal severe influenza season or during a pandemic situation, the number of deaths related to influenza and complications could reach 500,000 (FOX, 2005). Therefore, there is a large penalty for not having the proper amount of vaccine. The benefit of the Vaccine Model developed in this thesis would be to minimize the total cost of the vaccine purchased while covering as many customers as possible, and to minimize the risk of not having enough by distributing the purchase of the vaccine over several companies based on economic benefit. This problem is an example of a newsboy model, in which a single product is to be ordered at the beginning of a period and can be used only to satisfy demand during that period (NAHMIAS, 2001). A way of minimizing the effect of a shortage would be to order a little extra from multiple suppliers. This thesis identifies a model that can be used to determine the number of companies required to provide an adequate supply of the influenza vaccine to minimize the effect of an influenza vaccine shortage. Table 1-1 identifies the companies and vaccine products that are currently available in the United States. Due to the limitations in the amount of companies, the developed model does not utilize more companies than four for the production of inactivated influenza vaccine.

Table 1-1. Recommended Influenza Vaccines for Different Age Groups 2005

Vaccine	6Mo.	3 Yrs.	4 yrs.	5-49 yrs.	>50 Yrs
FluZone (Sanofi Pasteur, Inc.)		X	X	X	X
Fluvirin (Chiron)			X	X	X
FluMist (MedImmune, Inc.)				X*	
Fluarix (GlaxoSmithKline)				X**	X

\*FluMist is only for healthy individuals between 5 and 49 years of age.

\*\*Fluarix has been approved by the FDA for the 2005-2006 season for adults older than 18 years of age.

### E. DEADLY INFLUENZA SEASONS

Influenza A and B are the two types of influenza strains that cause human illness. Influenza B viruses are not categorized into subtypes. Influenza A viruses are categorized on the basis of their two surface antigens. Hemagglutinin (HA) is an antigenic glycoprotein found on the surface of the Influenza virus and is responsible for binding the virus to the cell that is being infected. Neuraminidase (NA) is an antigenic glycoprotein enzyme found on the surface of the Influenza virus. The three types of human influenza viruses are H1N1, H1N2, and H3N2. Influenza type A viruses are constantly changing and this requires the manufacture of a completely new vaccine batch each year.

Every year United States citizens die from infections caused by the influenza virus. Influenza and pneumonia were ranked number seven on the list of causes of deaths among the United States population in 2000 (CDC/NCHS, 2002). Usually, the virus each year only affects small children, the elderly, and those with existing medical conditions but three times in the last 100 years there has been an Influenza pandemic, or a world-wide epidemic, which has affected the United States. These were caused by new influenza A virus subtypes that emerged during the 20<sup>th</sup> Century. These new viruses spread around the world within one year of being detected. There were several other local epidemics that occurred that did not affect the United States.

#### Spanish Influenza

The first to affect the United States was the “Spanish Influenza” in 1918-19. The origin of the 1918-19 pandemic virus is not clear but it is believed to be caused by a type

A (H1N1) virus (SNACKEN, 1999). The Spanish Influenza epidemic caused an estimated 22 million deaths around the world according to the CDC. Over 12,000 deaths were reported in Philadelphia alone in September and October of 1918 (LYNCH, 1998). The disease caused a panic in Philadelphia because it hit healthy young adults. Half of the reported deaths were young healthy adults. Influenza A (H1N1) viruses still circulate today after being introduced again into the human population in the 1970s. In 1918, the influenza was helped by troop movements around Europe and the United States.

### **1. Asian Influenza**

In 1957-58 there was an influenza pandemic called the “Asian Flu”. The Asian influenza was caused by an influenza A (H2N2) type virus (SNACKEN, 1999). This virus was first identified in China in February of 1957 and spread to the United States in the summer of 1957. An estimated 1 million people died worldwide of the Asian influenza, 70,000 in the United States. A worldwide scare occurred in April of 2005 when this influenza virus strain was mistakenly sent out to 3,747 laboratories in 18 countries as part of their certification process. All parties were asked to destroy the virus upon receipt (CIDRAP, 2005).

### **2. Hong Kong Influenza**

The “Hong Kong Flu” occurred in 1968-69 and was caused by an A (H3N2) type virus (SNACKEN, 1999). It is estimated that 750,000 people worldwide died of the virus and 34,000 of those deaths occurred in the United States. Influenza A (H3N2) viruses still circulate today. Both the 1957-58 and 1968-69 pandemics were known to be caused by viruses containing a combination of genes from a human influenza virus and an avian influenza virus.

### **3. Avian Influenza**

The latest recorded multiple deaths resulted from the Avian Influenza A (H5N1) in China, Indonesia, Thailand, Vietnam, and Turkey with over 60 reported human deaths and 140 total cases. So far, this strain has not produced human to human infection. Another Chicken Flu or Bird Flu in Honk Kong, strain A (H5N1), in 1997 resulted in 18 confirmed human cases and 6 deaths (SNACKEN, 1999).

## **F. VACCINE DEVELOPMENT AND PRODUCTION**

### **1. Exact Influenza Vaccine Determination**

The Vaccines and Related Biological Products Advisory Committee (VRBPAC) of the Food and Drug Administration (FDA) meet each year to determine the formulation of the influenza vaccine in the United States for that year. The surveillance data is collected in January and February. The formulation for the vaccine is then agreed to by the committee around March based on observations conducted and the previous year's vaccine contents. The recommendations are based on antigenic analysis of recently isolated influenza viruses. Post-vaccination serologic studies are also used to develop the vaccine (MEADOWS, 2004). For example, the 2005 influenza vaccine includes two viruses that were used in 2004 (A/New Caledonia/20/99 (H1N1)-like and B/Shanghi/361/2002-like), and one new virus identified for this year (A/California/7/2004 (H3N2-like)). This formulation was agreed to in February 2005.

Each year after the virus strains are chosen by the VRBPAC, the task is then to develop the process to grow the strains in embryonated chicken eggs efficiently. In the 2003-2004 influenza season there were difficulties in the production of a certain strain of influenza virus, the H3N2 influenza A/Fujian/411/02, which was chosen to be used in the vaccine to combat the A/Fujian/411/02-like strain that was circulating that season. It was found that increasing the HA receptor-binding activity, balancing the HA and NA activities, helped increase production (LU, 2005).

### **2. Death Rates as a Product of Influenza Vaccine Supply and Distribution**

Influenza vaccine effectiveness depends on the age and the health, or immune status, of the patient being vaccinated. It also depends heavily on the match of the strains of the virus chosen for the vaccine for that year. The vaccine will be more effective if the strains used in the vaccine matches what is currently circulating in the United States.

The vaccine has been found to be 70% to 90% effective in preventing infection in healthy adults under 65 and 30% to 40% effective in preventing infection in adults over 65 based on the National Foundation for Infectious Disease reports (NFID, 2004) (ACPTF, 1994). The American Medical Directors Association (AMDA) reports that



generally the influenza vaccine is 50% to 60% effective in preventing influenza related hospitalization among those that are 65 and older, and 80% effective in preventing influenza related death among those that are 65 and older. These numbers were based on 64 different studies (AMDA, 2005).

### **3. Potential Influenza Vaccine Suppliers**

There are several companies in Europe and Asia that could be given a license to manufacture and distribute the influenza vaccine. The questions that have to be answered are; what is the current process that the FDA uses to qualify these companies and how much would the process cost? This should include a minimum order guaranteed by the government if there are not a sufficient number of companies identified with current licenses to manufacture and distribute the influenza vaccine in any given influenza season. The process could not be cost prohibitive. It would take too long to license them and get them to start production in an emergency so the list of companies must be developed in advance with some of the companies receiving orders to cover the potential need. This would put the United States government in the position of buying an amount to at least cover the cost of ramping up the production line on enough companies to have a sufficient vaccine supply.

For the 2005 influenza season there are three companies that have a license to provide inactive influenza vaccines in the United States. The companies are Chiron, Sanofi-Pasteur, and GlaxoSmithKline, all of which are in the United Kingdom. MedImmune in Gaithersburg, Maryland has developed the LAIV vaccine, which is also available for the 2005-2006 influenza season (CDC, November 2005). GlaxoSmithKline received a license under the new FDA fast track approval system in August 2005 to sell inactivated vaccine (USA Today, 2005).

### **4. Influenza Vaccine Production**

Production is determined by each individual private company that has a license. Requests for vaccines are made by health care providers and federal, state, and local governments. Some of the requests come from the Department of Veterans Affairs, long-term care facilities, acute care hospitals, children's health care providers, children's vaccine programs, the Department of Defense, and others. During the crisis in 2004,

those who vaccinated the most vulnerable were allowed to have the available doses. A pre-booking process is used to try to eliminate some of the uncertainty of the demand (CDC, Key Facts 2005).

The process of developing and manufacturing the annual influenza vaccine is a long one taking approximately six to eight months to complete (WOOD, 1998). The process starts in the autumn of the previous year with the identification of new antigenic variants. The appropriate strains are then chosen to be in the vaccine for the following influenza season. The generation of the appropriate reagents for the antigens is accomplished. Then the vaccine antigens are produced and purified. The antigens must be packaged and distributed. A yearly batch of influenza vaccine usually can not be used the following year and must be continually reformulated to keep pace with antigenic changes in the hemagglutinin and neuraminidase proteins of the influenza viruses. There is not time to restart the process. Therefore, a sufficient amount, usually more than is required, must be ordered at the beginning of the year. Due to the changing Influenza Virus there will always be some who are susceptible and die from the infection

The vaccine is produced in embryonated hen's eggs and requires the adaptation of an appropriate seed virus for high yield growth in the substrate in order to allow efficient production (TREANOR, 2004). Each egg must be hand inspected and hand injected. One egg grows 4-5 doses of vaccine. Millions of eggs are needed for the process. This process produces the inactivated vaccine administered by injection usually into the leg or arm muscle.

The process of using hen's eggs in the development of the influenza vaccine is laborious and ancient. There is also no room for alteration of the amount of the product once the process starts. The other problem with manufacturing the vaccine is that the cost is set and there is no room for negotiation. The profit margin is reduced making the market in the United States less attractive to potential manufacturers. A number of manufacturers left the market leaving only two to produce all the vaccine required in 2004 (BROWN, 2004).

In 2000, there was a disruption in vaccine delivery when two companies had trouble with production yields. There was no contamination. One of the influenza A(H3N2) vaccine components just had lower growth than expected (MMWR, 2000). In the recent history, only Chiron has had a plant closure that would disrupt vaccine production. A disruption risk like the one during the 2004 influenza season is therefore very slim. An act of terrorism would also add a small chance for disruption.

#### **5. Live Attenuated Influenza Vaccine (LAIV)**

A new version of the influenza vaccine called the Live Attenuated Influenza Vaccine (LAIV) was introduced into the market for the 2003 influenza season by MedImmune, Inc. of Gaithersburg, Maryland. MedImmune markets the vaccine under the name of Flumist. A type A and type B master donor virus (MDV) are identified. Then, the two MDVs each acquire the cold-adapted, temperature-sensitive, attenuated phenotypes through serial passage in viral culture conducted at progressively lower temperatures. The vaccine viruses in LAIV are reassortant viruses containing genes from these MDVs that confer attenuation, temperature sensitivity, and cold adaptation and genes from the recommended contemporary wild-type influenza viruses, encoding the surface antigens hemagglutinin (HA) and neuraminidase (NA). Thus, MDVs provide the stably attenuated vehicles for presenting influenza HA and NA antigens, to which the protective antibody response is directed, to the immune system (HARPER, 2003). The reassortant vaccine viruses are grown in embryonated hens eggs. Inactivated influenza vaccine contains only killed viruses, but the LAIV contains attenuated viruses still capable of replication. It is licensed in the United States for healthy persons between 5 and 49 years of age (GERBERDING, 2004). It has been shown to be ninety percent effective or higher for those who received one or two doses (HARPER, 2003). The vaccine is manufactured in hen's eggs so those who are allergic should not use this type of vaccine. In the case of an emergency the use of this live attenuated virus vaccine will free up the inactivated virus for those who are in the higher risk population if the use can be approved by the FDA for that use. However, a limited supply is currently manufactured by only one company. It is also more expensive than the inactive vaccine and must be refrigerated at 15° C or colder (HARPER, 2003).

LAIV was researched and initially included in the Vaccine Model development. This type of vaccine was initially thought to be able to save cost but due to the limited application in the specific age groups it turned out not to significantly affect the outcome of the model. The investment into vaccine doses that could be spread out over multiple age and risk groups was more effective when purchased. The first models developed did have the option of purchasing a maximum amount of LAIV influenza vaccine  $r_2$ . This was limited by the fact that there was only one producer of the vaccine type. The variable  $r_2$  was taken out of the model once it was determined that it was not cost effective. The cost of the LAIV vaccine or  $r_2$  is set by MidImmune, Inc., and for the 2005-2006 influenza season is set at \$20.70. LAIV could only supplement two age groups effectively, 5-19 Low-risk, and 20-49 Low-risk, and does not significantly change lead time for production.

## **6. Cell-Based Technologies**

A way to eliminate the use of the egg-based production is to continue to develop the new cell-based technology for the influenza virus production. Cell-based influenza vaccines use cells from mammals to grow the viruses used in the vaccines. Using the cell-culture method allows those allergic to eggs the ability to receive the vaccine. It also eliminates the use of the step to adapt the virus to grow in the eggs. This makes the process quicker and provides a much needed surge capacity. Cells may be frozen and then grown quickly in large volumes when required (USD HHC, 2005). There are three cell-based influenza vaccines that are close to receiving regulatory approval in Europe and the United States. One of these was developed by Protein Sciences Corporation, a biotechnology company in Meriden, Connecticut. No live influenza viruses are used. The process also eliminates the need for preservatives like thimerosal. This vaccine development could be on the order of weeks instead of months (FLUBLØK PRESS, 2004).

In November 2005, President Bush outlined his new strategy to fight potential pandemic influenza which included \$2.8 billion dollars earmarked to speed the development of vaccines (USA Today, 2005).

## 7. Anti-Viral Treatments

Antiviral drugs for influenza can be used as an addition to the influenza vaccine for controlling and preventing influenza. However, anti-viral treatments are not a substitute for vaccination. Antiviral drugs are used to treat influenza type infections early. Four licensed influenza antiviral agents are available in the United States: amantadine, rimantadine, zanamivir, and oseltamivir. Amantadine and rimantadine work on the influenza type A. Zanamivir and oseltamivir work on influenza type A and B.

In a study conducted in August of 2005, Balicer, Huerta, Davidovitch & Grotto analyzed strategies for the use of stockpiled antiviral drugs in the context of a future influenza pandemic and the estimated cost benefit ratios. Balicer et al. estimated the health related impact of a pandemic influenza on the Israeli population by using illness, hospitalization, and death rates from previous pandemics. They found that a pandemic would result in 2,855 deaths, \$55.4 million in health-related costs, and \$523.5 million overall cost to the economy ( $\approx 0.5\%$  of the Israeli gross domestic product). Israel is a country of 6 million inhabitants

In the course of their research, three different ways of distribution of prophylaxis were identified. The research concluded that stockpiling of drugs will produce cost savings to the government of Israel no matter what strategy is used for their deployment. It was also found that the process would return dollars invested by almost a 4 to 1 margin (BALICER et al., 2005). A stockpile of antiviral drugs could also reduce deaths, hospitalization, and missed days at work during an influenza pandemic.

The Avian bird influenza epidemic (H5N1) has forced the United States to start stockpiling antiviral drugs, specifically the Tamiflu brand of the oseltamivir antiviral drug that seems to work against the H5N1 strain (CBO, 2005). This is just in case the Avian bird influenza virus changes and can be passed from human to human. This has caused Roche Pharmaceutical Company to halt shipment to private companies in the United States in October 2005 to so that it would not affect the global supply (AP, 2005). Tamiflu is a neuraminidase inhibitor and can be used if the patient has had symptoms for

two days or less. It attacks the influenza virus and slows or stops the virus from spreading inside the body. Tamiflu can treat some types of influenza and associated illnesses.

#### **8. Lower Dose Distribution**

Another way to stretch the influenza vaccine in a shortage is to deliver a smaller amount of the influenza vaccine to each individual. Studies have found that one half of the standard dose of trivalent influenza vaccine administered by injection into muscle produced the same immune response of those given the full dose (TREANOR, 2002). Subjects who were older than 60 years of age still saw a good response to the smaller dose (LA MONTAGNE, 2004).

#### **G. CHAPTER SUMMARY**

The history of recent influenza seasons has shown us that the supply of the influenza vaccine is variable and the amount of customers searching for the vaccine also varies. History also teaches us that any one year could be devastating if a pandemic develops. The question to be answered is how many influenza shots should be ordered to avoid a shortage assuming a normal influenza season to cover as many customers as possible, and to minimize the overall cost of vaccination orders and lost earnings from all deaths keeping in mind that a pandemic could occur. The number of vaccines ordered should minimize cost while covering the demand. After the United States Strategy to fight a future pandemic influenza was outlined by President Bush in November of 2005 he was immediately criticized for only requesting that 20 million doses of the influenza vaccine be stockpiled against the current strain of bird flu H5N1. (USAToday, 2005) The critics missed that the cornerstone of the strategy would be to develop the ability to produce new vaccines quicker. Until the companies that provide the influenza vaccine have the ability to produce the vaccine at a much more rapid pace hard choices have to be made in terms of who gets the vaccine when there is a limited supply. During a normal influenza season and also during a pandemic situation a number of people will die no matter how much vaccine is produced and distributed. However, lives can be saved by having the ability to produce the vaccine required quickly and distributing it

appropriately. Until the time that we can produce the influenza vaccine with a quicker response time, it is important to understand the production and distribution process including the supply and demand of the influenza vaccine.

## **II. VACCINE SUPPLY AND DEMAND**

### **A. INTRODUCTION**

The problem of influenza vaccine production and distribution involves several complex issues. Understanding the supply and demand chain for the influenza vaccine is helpful in developing an optimized model for ordering the correct amount of vaccine each year. (FORSBERG, 2000) The uncertainty in production amounts, the uncertainty in customer demand, and the supply and demand chain all add to the problem of getting the influenza vaccine to where it is needed each year. The architecture of the influenza vaccine distribution system, including inflow and outflow requirements, is analyzed in this thesis by utilizing the rational method (MAIER, 2002). Mathematical principles, equations, and estimated costs associated with potential deaths are utilized to develop an optimized solution.

### **B. SUPPLY**

The CBO identified several problems in the influenza vaccine supply chain (CBO, 2005). The lengthy egg-based manufacturing process means that production cannot be scaled up. Demand for the vaccine each year varies and can depend on outside factors like the severity of the previous year and media coverage. Demand for flu vaccine is variable and cannot be stored from one flu season to another. The manufacturing process is prone to contamination. The government accounts for less than 20% of the market for the influenza vaccine. Few manufacturers of influenza vaccine serve the United States because of the problems identified above (CBO, 2005).

#### **1. Individual Company Reliability History**

Each individual company has had manufacturing problems that have either slowed production or resulted in lost batches of vaccine due to contamination. Some have had to close their plant for FDA recertification after contamination problems. There have been problems in three of the last five years resulting in delays in the number of vaccine produced (MMWR, 2005). This is due to the difficulty in the production process.



## **2. Production Requests**

The United States market is by far the largest demand of influenza vaccine for the world's producers. The United States population is around 300 million (U.S. Census Bureau, International Data Base, 4/26/05) which is larger than the population of the whole of the European Union and 10 times greater than Canada. The target supply for the United States is somewhere between 68 million and 99 million doses of the influenza vaccine (CDC, June 2005).

## **3. Company Response to Orders**

The number of influenza vaccine doses produced in any given year is limited by the capacity of the production facilities, the availability of eggs used for the production, and the yield of influenza virus from each egg. All three of those variables can be easily disrupted. Private companies are required to plan the amount of vaccine they will produce well in advance. Any disruption of the production schedule may lead to a delay in the availability of the vaccine and result in a customer relation nightmare. The manufacturing process is currently very rigid and does not allow much room for error in ordering. When the influenza strains are identified and the formulation is complete the orders must be placed or there will not be enough vaccine when it is needed. A significant part of the problem is the liability concerns. Financial disincentives and government regulations have caused a number of companies to leave the vaccine market. In 1957 there were 26 companies that manufactured the influenza vaccine. There were 12 companies 30 years ago that manufactured vaccine. Back in 1999 there were four. Now, we are lucky to have the three that manufacture inactive influenza vaccine and one that manufactures the LAIV vaccine. The demand is also problematic and fluctuates based upon the type of influenza season. Vaccines are not viewed as profitable to companies because the market is limited in comparison to the general drug market. They are also tough to develop due to the fact that they change every year.

## **C. DEMAND**

### **1. Normal Season Demand**

In a normal influenza season the demand in the United States for the influenza vaccine is usually 75 to 100 million doses depending on the severity of the season (CDC, June 2005). In a pandemic situation that number would at least double to 180 million.

The amount of 185 million comes up frequently as the number of vaccine doses that the CDC would like to have on hand or at their disposal during the regular influenza season (CLARK, 2005). This number would allow the vaccination of all the elderly, infants, and health care workers as well as those in all categories who request it.

The influenza vaccine market would be considered a small market to most large pharmaceutical companies. Total global market sales are around \$6 billion dollars for the influenza vaccine. That is small compared to global sales of drugs which are \$340 billion. The combination of the demand fluctuation, the limited market, and the potential for manufacturing difficulties makes the vaccine market very risky.

## **2. Demand Fluctuations**

The demand for the vaccine fluctuates from year to year. The most influenza shots ordered prior to 2005 was 83 million (CLARKE, 2005). In 2004, only 57 million doses were eventually distributed. In 2005, the estimate for vaccination production with production from three companies will be from 71 million to 97 million doses (CDC, September 2005). Table 2-1 identifies the amount of vaccine produced and sold for each year starting from 1999. Some years there is not enough demand and the vaccine goes unsold. When there is a shortage as in 2004-2005 healthy individuals refrain from the vaccine which can result again in unused vaccine. With the price set by the government, it can not be raised to take into account the higher risk in the market. This potentially drives companies out of the vaccine production business. There should be a price and quantity curve, which is not there if the government sets the price of the vaccine like a commodity (PERREAULT, 2005).

Table 2-1. Influenza Vaccine Production and Demand

Year	Production (million)*	Over/Under (million)
1999-2000	77	3** (MMWR, 2000)
2000-2001	75	<1
2001-2002	87	8** (CDC, 2003)
2002-2003	79	<1
2003-2004	87	<1
2004-2005	60	3*** (BECKER, 2005)
2005-2006	68-99	-

\*Production numbers taken from CDC Influenza Vaccine Bulletins for the corresponding years.

\*\*Production not actually used.

\*\*\*Estimated unused due to healthy persons refraining from the vaccine.

#### **D. DISTRIBUTION**

The influenza vaccine system for the United States will be identified as comprised of the Government and Health Care industry that requests the vaccines for patients and the companies that manufacture the vaccine. In the middle of the two is the distribution process which includes private distribution companies. These private distribution companies search out vaccine supplies after all the direct orders have been purchased through the manufacturers and act as a clearinghouse for any vaccine remaining at the manufacturing facilities. The amounts a purchaser pays may differ depending upon such variables as the quantities purchased, contractual arrangements, and source of purchase. The Congressional Budget Office identified the distribution process as inadequate (CBO, 2005).

##### **1. Private Distributors**

Private companies purchase the vaccine to either resale or to keep the doses for their own use. This results in many instances in localized shortages. Including the companies that manufacture the vaccine there are 27 private influenza vaccine distributors listed on the Health Industry Distributors Association website where doses of the vaccine can be purchased. The CDC recommends that several potential vaccine suppliers should be researched to find the vaccine.

##### **2. Government**

Government entities including state and local federal immunization grantees and county and city health departments directly order the vaccine and must make a good

estimate of their requirements for the vaccine well in advance of the influenza season. They can order directly from the manufacturer prior to the influenza season. Usually that pre-booking activity closes around the beginning of June prior to the influenza season. After the season is underway private distributors are used to deliver any additional vaccine doses that are available. Only 20% of the vaccine is ordered by the United States Government and therefore, the Government has little say in how the vaccine is distributed and used.

### **3. Health Care Providers**

Health care providers must make a good estimate of their requirements for the vaccine as well. Physicians with practices, hospitals, nursing homes, and pediatric care facilities all have to provide their requirements so that enough vaccine will be produced. 80% of the orders are sent to private institutions. The CDC recommendations on distribution and use of the vaccine to certain high risk groups are only used as recommendations. It is up to the health care provider to determine who receives the influenza vaccine.

### **4. Distribution Problems**

The United States has experienced a disruption in the manufacture or distribution of inactivated influenza vaccine during three of the last five influenza seasons (MMWR, 2005). During the 2000-2001 influenza season there was a shortage of the influenza vaccine due to the fact that production yields of the influenza type A (H3N2) strain were lower than expected. There were also other manufacturing problems at two of the companies that made the vaccine. This only delayed the delivery of the vaccine from the projected October 2000 to December 2000. Due to this there were three million doses that went unused. Vaccination efforts were focused on the elderly over 65 and those with cardiovascular disease or other illnesses that made them more susceptible to the influenza virus. The problem occurred early in the influenza season so there was a delay of delivery of the vaccine but it did not have an overall negative affect.

The other recent major production difficulty occurred during the 2001-2002 influenza season. Twenty-six million doses that were supposed to be delivered by October 2001 did not arrive until November and December of that year. That season saw

an 8 million vaccine overproduction due to the late arrival of the vaccine. At the end of the influenza season, there were still vaccines not sold. Only 79 million doses of the vaccine were used (CDC, 2003) when 87 million were produced (CDC, 2001).

The changing amount of vaccine doses that are used, the vaccine manufacturing process, and the government approval process affect the system. There are several companies that manufacture and distribute the vaccine in Europe that could provide the vaccine in the United States if they go through the approval process. The approval process must be identified as a roadblock to increasing the number of companies available to manufacture and provide influenza vaccine in the United States. Only one company came into the United States vaccine market in 2005.

Companies respond to orders placed prior to the start of the influenza season and additional orders during the season until their supply runs out. Currently, under the system as it is set up, there is no means of being flexible to additional requests for a more severe season or a pandemic situation. Therefore, there must be several companies in place before the influenza season that can produce the amounts required.

##### **5. Free Market versus Uniform Distribution in Other Countries**

The United States uses the free market to purchase and distribute the influenza vaccine just like any other product. The supply for each influenza season is based on demand from previous years and the pre-booking orders that are provided by the government vaccine distributors and health care workers. Private companies who are licensed to manufacture the vaccine determine first if it will be cost effective to manufacture the vaccine and then how much they will produce. As long as the egg based system is used to develop the vaccine a steady demand known in advance is necessary to drive production in a free market. Once the vaccine is produced then it falls into the distribution system which should be monitored to ensure that the vaccine gets to those who need it. In some instances the big purchaser seems to be favored over the small purchaser and often the ability to shift vaccine from areas with an over supply to areas with local shortages has been difficult due to many suppliers and no single clearinghouse or distribution point.

Canada is the only country that vaccinates more of a percentage of its population than the United States. This is accomplished through programs implemented by the Canadian Coalition for Immunization Awareness & Promotion (CCIAP). The goal of the CCIAP is to help ensure that all Canadians are aware of the importance of immunization and that all Canadians are properly immunized. Each province in Canada has taken the influenza vaccine program as a high priority. In Ontario, the “Ontario Experiment” is under way with the Canadian Government offering the influenza vaccine free to all who want it. In three provinces in Canada, including Ontario, the vaccine is offered free of charge to all customers. It is also offered free to the high-risk groups in the other provinces with an overall total vaccination rate for Canada of around 27% (CBC, 2005). With the smaller amount of total population, around 33 million, it is easier for Canada to distribute the vaccine.

Dr. Julie Gerberding, (CDC, 2005) of the CDC in a press conference in November, 2005 admitted that, “the vast majority of flu vaccine is in the private sector and we have very little capacity to move vaccine around. So, what we are doing is preparing our own stockpile of vaccine, getting about 800,000 doses of vaccine from Chiron at the end of November (2005), and we'll use those doses to help offset shortages in communities where there is no one with vaccine available”. In October 2004, when there was a severe shortage of vaccine no one single entity knew how much was available, where it was, and who needed it most. A simple information-sharing system was developed but that did not help the problem of local officials deciding person by person who should get the vaccine. Distribution and tracking of the vaccine could be vastly improved if each state or region would develop a single entry point and a better tracking system to ensure that the vaccine gets to where it is needed.

## **6. Simplified Model**

A simplified distribution system is used to model the manufacturing, distribution, and use of the influenza vaccine. For the model, each company is considered to have one batch of vaccine that they produce. This makes the vaccine for that company good or bad and not partially good or bad. Chances are that if there is a manufacturing problem or contamination it will shut down the plant. A delay will be modeled as a good batch that

arrives in time to utilize. The model also simplifies the distribution to eliminate the private distributors and focuses on the manufacturer to health care provider line. The assumption is that the vaccine will find the paying customer if there is still vaccine left in the market.

#### **E. CHAPTER SUMMARY**

The system for the production of the United States supply of flu vaccine has been affected over the last few years by supply shortages. Each year influenza vaccine production is a complex process with little room for error. The process of vaccine component production and filling a vaccine request can take up to nine months. The companies that can sell the influenza vaccine in the United States are limited. The demand is up and down based on a mild or severe year for influenza infections. Sometimes the companies sell out of vaccine, other years they go unsold adding additional risk to a small overall market. The difficult manufacturing process, the limited time to identify and manufacture the product, government regulations and license requirements all lead to a high risk situation for any commercial company that manufactures the influenza vaccine. The problems in production, the difficulties in the distribution of the vaccine, and the demand uncertainty were reviewing the current system architecture and were taken into account when developing the new model to distribute the influenza vaccine. The next chapter introduces a new Vaccine Model developed as part of this thesis research to combat the problem of purchasing and distributing incorrect amounts of influenza vaccine each year.

### **III. VACCINE MODEL**

#### **A. VACCINE MODEL INTRODUCTION**

This chapter introduces the Vaccine Model developed as part of this thesis research. The Vaccine Model can be used to identify the correct number of vaccines to be ordered from each company. The vaccine order quantities are based on the number of companies available for the production of the influenza vaccine and divided equally between those companies to minimize overall cost. The Vaccine Model determines the number of customers based on the population of the United States and their age, and then determines how many companies are needed to spread out the purchase to ensure that enough is available for the determined amount of customers. Finally, the Vaccine Model then determines which age groups should receive the vaccinations first to minimize total cost. A goal of this thesis research is to help minimize cost while providing sufficient vaccinations to those who request it.

The Vaccine Model calculations are implemented in Excel and calculations are produced using the Frontline's Solver in Microsoft Excel. The total cost of the vaccine program cell is minimized. The total cost includes the cost of the vaccine purchased and the cost of the deaths associated with the influenza virus. Two policies were used in the distribution of the vaccine. One policy uses a strict priority that was developed for the distribution of the vaccine. The other policy would be to distribute the vaccine by population percentage as the customers came to receive the vaccine. The Vaccine Model is also used to look at a pandemic situation in which more than usual percentages would request a vaccine in each age group identified.

The Vaccine Model is primarily developed on the basis of the number of customers. The number of potential customers is based on the population of the United States and is set at 80,679,143 as a default. The number is developed by dividing the total population of the United States into age groups and using the past percentages of vaccination in each age group to determine the potential total customers. This number can be changed by changing the observed percentage of each age group that requests a vaccine.



## **B. VACCINE MODEL DEVELOPMENT AND DISTRIBUTION POLICIES**

The Vaccine Model is primarily developed on the basis of the number of customers. Customers are defined for the purpose of the model as the total number of United States citizens that request a vaccine. Non-customers are defined as the United States citizens that do not actively seek a vaccination during the influenza season. The customers are divided into age groups and are placed into high-risk or a low-risk category. On any given influenza season the number of customers requesting vaccination ranges from 70 to 90 million depending on the severity of the season. In a pandemic situation that number would at least double to 180 million. The amount of 185 million comes up frequently as the number that the CDC would like to have on hand or at their disposal during the regular influenza season (CLARK, 2005). This number would allow the vaccination of all the elderly, infants, and health care workers as well as those in all categories who request it.

The Vaccine Model calculations are used to determine how many companies are required and how many vaccine doses from each company should be ordered to have an adequate supply of vaccine on hand during the influenza season. It is important to get a large amount of the vaccine out to the public as early as possible due to the tapering off of customer demand because the influenza season usually peaks in February (YEE, 2005). The mortality rate also peaks by the end of February (EURO, 2001). The hope is that the free market and the increase in the fair market price of the vaccine agreed upon by the United States Government will entice private companies to invest in the market (CDC, June 2005). The total United States population data was gathered from United States Census (2000). The Vaccine Model is set up using the indices, parameters, decision variables, constraints, and objective function below.

The indices used in the Vaccine Model are:

$i$  = Customer category ( $i=1, 2 \dots 10$ )

$j$  = Customer category ( $j=1, 2 \dots (i-1)$ )

$n$  = Number of companies with a bad vaccine batch ( $n=1, 2, 3, 4$ )

$N$  = Number of companies total ( $N=1, 2, 3, 4$ )

$R$  = Number of doses of vaccine purchased ( $R \geq 0$ )

The parameters used in the Vaccine Model are:

- $A$  = Influenza virus attack rate for all people in all age groups
- $Cost_F$  = Cost of those that die without ever looking for a vaccine
- $C_i$  = Cost of death based on age for each customer category
- $D_{nNR}$  = Cost of all vaccinated and unvaccinated customer deaths
- $f_1$  = Cost of the total vaccine purchased
- $f_2$  = Cost of all those that die that requested a vaccine but did not get one
- $f_3$  = Cost of all those that die that requested a vaccine and were given a vaccine
- $n$  = Number of companies with a bad vaccine batch
- $P_{nN}$  = Probability of contamination of a company vaccine batch
- $Q_i$  = Probability of death for unvaccinated customers
- $Q_i'$  = Probability of death for vaccinated customers
- $Q_{Xi}$  = fraction of the unvaccinated, attacked population in age group  $i$  that dies
- $Q_{Xi}'$  = fraction of the vaccinated, attacked population in age group  $i$  that dies
- $X_{inNR}$  = Total number of customers in group  $i$
- $X_{jnNR}$  = Total number of customers in group  $j$  already vaccinated (strict priority)
- $T$  = Total number of customers in the United States
- $TotalCost$  = Total cost of all vaccine purchased and all deaths
- $V$  = Cost per inactivated influenza vaccine
- $Y_{inNR}$  = Total number of customers vaccinated in group  $i$

The decision variables used in the Vaccine Model are:

- $N$  = Number of companies required to minimize cost
- $R$  = Number of vaccine to be purchased to minimize cost

The equation that is minimized is:

$$TotalCost = E(f_1(n, N, R) + f_2(n, N, R) + f_3(n, N, R)) + Cost_F \quad \text{Equation 1}$$

Subject to the constraints:

$$R \geq 0, N \geq 0 \quad \text{Equation 2}$$

The Decision variables for the Vaccine Model are the total inactivated vaccine purchased  $R$ , and the total number of companies to purchase the vaccine from  $N$ . The variable  $n$  is the number of companies that develop a bad batch of vaccine that can not be used. If the vaccine can not be used it will not be delivered, and therefore, not paid for. The  $N$  value must be smaller or equal to the number of companies that currently have a license to sell vaccine in the United States market.

Parameters for the Vaccine Model include the cost per inactivated influenza vaccine dose  $V$ , the total number of customers  $T$ , which is the sum of the customer totals

of each age subgroup  $X_{inNR}$ , the number of companies that fail to produce useable vaccine  $n$  from a total number of  $N$  companies, the probability of contamination with each order of vaccine  $P$  (see Table 3-4), the probability of death given a vaccine shot  $Q_i'$ , and the probability of death given no shot for low risk and high risk customers  $Q_i$ , and the total number of customers receiving a vaccine  $Y_{inNR}$ . The percentages of each age group in the general United States population and the percentage of those in each age group requesting vaccination on any given year divided by high and low risk groups is used to determine the number of customers that will require an influenza vaccine. The Vaccine Model is primarily developed on the basis of the number of customers. The number of potential customers  $T$  is based on the population of the United States and is set at 80,679,143 as a default. This number is developed by dividing the total population of the United States into age groups and using the past percentages of vaccination in each age group to determine the potential total customers. This number can be changed by changing the observed percentage of each age group that requests a vaccine. The cost of the inactivated influenza vaccine  $V$  as set by Medicare's 2005 Physician Fee Schedule was \$18.31 (CDC, 2005).

The question to be answered is how many influenza shots should be ordered from a set number of companies to minimize the effect of a shortage, to cover as many customers as possible, and to minimize the overall cost of vaccination orders and lost earnings from all deaths. The number of vaccines ordered should minimize cost while covering the demand. Until the companies that provide the influenza vaccine have the ability to produce the vaccine at a much more rapid pace hard choices have to be made in terms of who gets the vaccine when there is a limited supply. During a normal influenza season and also during a pandemic situation a number of people will die no matter how much vaccine is produced and distributed. However, by having the ability to produce the vaccine required quickly and distributing it appropriately lives can be saved and the overall death toll and cost for the United States can be minimized. These two objectives, minimizing the death toll and minimizing the overall cost to the country, will contradict each other. With an endless amount of vaccine the amount of deaths will be limited to a

fraction of those who do and do not search out a vaccine. With no funds and no program to distribute the vaccine there will be many more deaths that will cost the country and individual families lost providers and wages.

Two policies are looked at in terms of purchasing the vaccine doses. These policies determine which customers receive the vaccine doses available in the Vaccine Model. The first policy is to vaccinate the population as they arrive based on the percentage that request vaccination. This is a real world scenario and would be the normal way that the vaccine is distributed. Every year there are target groups by the CDC to receive the vaccine but the majority of the vaccine is distributed to the customers that search for it. The second policy provides the vaccination to only those in high risk groups first, using the required amount to cover all high risk groups, then to distribute to the lower risk groups if there is any remaining. This type of strict priority policy could be used in a shortage situation to minimize deaths due to an unforeseen shortage.

### **C. VACCINE MODEL AGE CATEGORIES AND PRIORITY**

Age categories have been identified for use in modeling affects of influenza. Meltzer (1999) identified 0-19 years, 20-64 years, and 65+ years. These categories were assigned present value earnings lost by Meltzer, as well as illness and hospitalization costs.

Table 3-1 identifies each age category and the percentage of each age category in the total population of the United States (U.S. CENSUS, 2000). The percentage of high-risk and low-risk customers from each age group based upon the United States population is shown in Table 3-2. This table is based on the past percentages of customers (i.e. persons looking for an influenza vaccine). The average number of persons in each age category requesting a vaccination varies but is estimated by past percentages. The vaccination percentage has been significantly improved along with other childhood disease vaccinations for young children at 81% for 2003-2004 (FOX, 2005). The percentage of adults 65 years and older that are vaccinated ranged from 40% to 70% in 1999, but has increased to 60% to 70% in 2005. (MELTZER, 1999; and ZWILLICH, 2005).

For each age category and risk level in Table 3.2, the percentage of those in each age group who usually request vaccination in the United States was multiplied by the number of persons in each category to determine the potential number of customers  $X_{inNR}$  that would show up at a distribution point for a vaccination.

Table 3-1. Age Categories and Related United States Population

<b>Age</b>	<b>US Pop (Mil)</b>	<b>US Population Percentage</b>
0-4	19.18	6.82%
5-19	61.30	21.78%
20-49	124.09	44.10%
50-64	41.86	14.87%
65+	34.99	12.43%

The health impact of individual seasons can vary widely on the basis of the size of the susceptible population, the prevalence of influenza infections, the type and strain of the annual viruses introduced into the population during the influenza season, and the match between the current virus strains and the strains used in the vaccinations. The Vaccine Model estimates how many customers in each group will likely request a vaccine based on population of the United States and the population of each age group.

Two policies for the distribution priority of the vaccine are used in the Vaccine Model. The strict priority distribution policy uses a rigid priority to distribute the influenza vaccine. If the higher risk groups are targeted first in a set strict priority, and the distribution is limited to those groups only, you can limit the deaths associated with a shortage of the vaccine and overall cost. A study of the percentage of persons in each category, the potential for death, and the cost of death associated with each age category was accomplished to develop a priority of vaccination. This priority of vaccination, based on the calculated probabilities of death, is identified in Table 3-2. Additional information on the probabilities of death is provided in the next section and in Table 3-3. The vaccination priority in Table 3-2 was used strictly in the Vaccine Model to distribute vaccine first to the high risk groups that will reduce expected total cost. This form of

distribution could be used in an influenza vaccine shortage or pandemic situation in which there was not enough time to produce additional vaccine to cover the increased demand.

The percentage distribution policy provides the vaccine to customers as they request it. In a normal influenza season, customers come to request vaccine based on their age categories and risk group. Each age and risk group has a percentage that searches for a vaccine as identified in Table 3-2. The vaccine is then distributed based on the percentage of customers that request a vaccine. No one group is completely vaccinated but the majority of all high risk groups are vaccinated.

Table 3-2. Customer Age Group and Risk Categories, Vaccination Percentage, and Total Customers

<b>Customer Category (i)</b>	<b>Category Name</b>	<b>Percentage of Age Group</b>	<b>Total US Population</b>	<b>Vaccination Customer Average in US</b>	<b>Total Customers (X<sub>i</sub>) million</b>
1	0-4 Years Old HR	6.4%	1.23	81% (Fox, 2005)	.994
2	5-19 Years Old HR	6.4%	3.92	24% (Zwillich, 2005)	14.542
3	20-49 Years Old HR	14.4%	17.87	24% (Zwillich, 2005)	.942
4	50-64 Years Old HR	14.4%	6.03	37% (Zwillich, 2005)	8.607
5	65+ Years Old HR	40.0%	13.99	70% (Fox, 2005)	4.289
6	0-4 Years Old LR	93.6%	17.95	81% (Fox, 2005)	15.933
7	5-19 Years Old LR	93.6%	57.38	15% (MMWR, 2005)	2.230
8	20-49 Years Old LR	85.6%	106.22	15% (MMWR, 2005)	10.750
9	50-64 Years Old LR	85.6%	35.83	30% (MMWR, 2005)	9.797
10	65+ Years Old LR	60.0%	20.99	60% (MMWR, 2005)	12.596
<b>Total</b>			<b>281.42</b>		<b>80.68</b>

#### D. INFLUENZA VIRUS ATTACK AND DEATH RATES

$Q_{xi}'$  is the fraction of the vaccinated, attacked population in age group  $i$  that dies due to the influenza virus.  $Q_{xi}$  is the fraction of unvaccinated, attacked population rate of deaths due to the influenza virus. The Attack Rate  $A$  is the attack rate in the United

States for all people in all age groups and is assumed to be homogeneous across all age groups and risk categories. The attack rate is defined as the percentage of the United States population, customers and non-customers, which will be attacked by the influenza virus strain during the influenza season. In the Vaccine Model, the normal influenza season is modeled using a 20% attack rate (MELTZER, 1999; LEE, 2006; GERDIL, 2003; CBO, 2005). The attack rate multiplied by the percentage of each population death rate if attacked gives the fraction of each age group that dies of the influenza virus.

The overall death rates used by the Vaccine Model are taken from Meltzer (1999) and are considered the upper bound of the expected death rates. These death rates are identified in Table 3-3 and are not homogeneous.

The effectiveness of the influenza vaccine is a topic for discussion. The Advisory Committee on Immunization Practices (ACIP) stipulates that the effectiveness of the inactivated influenza vaccine depends “primarily on the age and immunocompetence of the vaccine recipient and the degree of similarity between the viruses in the vaccine and those in circulation.” (MMWR, 2005). The effectiveness of the vaccine is dependent upon the health of the person being vaccinated and the guess made of the influenza strains that will be circulated during the influenza season. Studies have shown that the vaccine was 58% to 91% effective in combating illness in children, 22%-54% effective in children with one high risk factor, 60%-78% effective in older children with one high risk factor, 52%-90% effective in healthy adults younger than 65 (attributed to good or bad virus matching), 38% effective with those adults that have one or more high risk factors, and 30% - 70% effective with those adults that are older than 65 (MMWR, 2005). Other studies have found less benefit after vaccination. Taking into account the barriers to effectiveness and the past studies completed, an estimation of the vaccine effectiveness was developed and used in the Vaccine Model. The percentage used for vaccination effectiveness in the Vaccine Model is 60%. This assumption can be changed when definitive numbers are produced by the CDC. This is slightly lower than the published CDC number of 70% (MMWR, 2005).

The customer category is based upon cost per loss of life in that age category generated by the Vaccine model explained below in Section F of this chapter. The cost per loss of life is highest for 0-4 and 5-19 high risk age group, and is lowest for the older than 65 low risk group. The customer category rank is shown in Table 3-3.

The overall death rates for unvaccinated customers  $Q_i$  is given by Equation 3 below.

$$Q_i = Q_{Xi}^A \tag{Equation 3}$$

Table 3-3 shows overall death rates for the 10 age and risk groups.

Table 3-3. Age Categories and Death Risk Probabilities

Age	Risk Level	Death Rates*	Customer Category (i)	$Q_i$ (unvaccinated)	$Q_i'$ (Vaccinated)
0-4 years	High	7.65	1	.00153	.000459
0-4 years	Low	0.125	6	.000025	.000015
5-19 yrs.	High	7.65	2	.00153	.000459
5-19 yrs.	Low	0.125	7	.000025	.000015
20-49 yrs.	High	5.72	3	.001144	.0003432
20-49 yrs.	Low	0.09	8	.000018	.0000108
50-64 yrs.	High	5.72	4	.001144	.0003432
50-64 yrs.	Low	0.09	9	.000018	.0000108
65+ yrs.	High	5.63	5	.001126	.0004504
65+ yrs.	Low	0.54	10	.000108	.0000756

\*Death Rates are taken from Meltzer (1999) per 1,000.

#### E. COMPANY RATE OF BATCH CONTAMINATION

An estimate for the probability of contamination is required for the Vaccine Model due to the uncertainty of the manufacturing process. A 10% estimate of batch contamination was used. The probability of contamination with each vaccine order  $P$  is shown in Table 3-4 for one, two, three, and four companies. The probability of a good batch with each vaccine order would then be  $(1-P)$ . The probability of a bad batch given an order is modeled as a binomial distribution where  $P_{13}$  is the probability that one batch



is bad when you order from three companies. The influenza vaccine production was significantly slowed or reduced by contamination or manufacturing problems three times between 2001 and 2005. Therefore, a ten percent probability is a reasonable estimate for  $P$ .

Table 3-4. Binomial Probabilities for Individual Company Contamination

Binomial	Probability of Contamination				
	0	1	2	3	4
$P_{nN}$					
$P_{n1}$	0.9	0.1			
$P_{n2}$	0.81	0.18	0.01		
$P_{n3}$	0.729	0.243	0.027	0.001	
$P_{n4}$	0.6561	0.2916	0.0486	0.0036	0.0001

#### F. VACCINE MODEL DEATH COSTS

The goal of the Vaccine Model developed for this thesis is to minimize the cost of death and the cost of the vaccine used under the current situation of limited resources and a time constraint for the production of the vaccine. The only way to do this is to identify an amount of money for each potential life lost and then use that to develop a function based on those dollar amounts, and then minimize it based on the amount of deaths using a certain amount of vaccine and the cost of the vaccine program itself.

For each age category, Meltzer (1999) placed a price on the lost wages over a lifetime of persons that have died. The average cost of a death in 1995 US dollars of one under 19 was \$1,019,536, 20-64 years was \$1,045,278, and only \$74,146 for someone 65 years old and older. The cost of death was estimated in 2006 by Lee at \$1.9 million for those under 19 years of age, \$1.8 million for those 20-64 years of age, and \$190,000 for those 65 years and older (LEE, 2006).

Some critics of the vaccine priority list developed by the CDC say that younger individuals should be given priority over the elderly for vaccination. They argue that vaccine effectiveness is less for older individuals and younger individuals play an important role in the supply chain for food, etc (COWEN, 2005).

For the Vaccine Model, the cost of death parameters  $C_i$  are estimated at \$1,000,000 death cost for all persons in customer categories under 65, and \$75,000 for all persons in customer categories 65 years of age and older. The focus of this thesis is on the cost of death and developing a number of available vaccines so that the right amount of vaccine is provided to each age group to reduce potential deaths.  $C_i$  could be calculated for each age group resulting in a prorated  $C_i$  for all ages which could then be inserted into the calculations. Calculations would be based on annual earnings and work histories for low and high risk customer categories. The use of a prorated  $C_i$  would greatly increase the utility of the Vaccine Model and is considered for future research.

### G. VACCINE MODEL STRUCTURE

The Vaccine Model needs to solve the problem of selecting  $(R, N)$  to minimize the expected value of the cost of the vaccine purchased  $f_1$ , the cost of those dying after they receive a vaccine  $f_2$ , the cost of those dying that did not receive a vaccination  $f_3$  after requesting it, and the cost of those dying that never looked for a vaccine,  $Cost_F$ . Thus, the equation to minimize is;

$$TotalCost = E(f_1(r, n, N) + f_2(r, n, N) + f_3(r, n, N)) + Cost_F \quad \text{Equation 1}$$

The constant  $Cost_F$  is the cost associated with the non-customers, the population that does not seek a vaccination. This is calculated by multiplying the amount of population not seeking a vaccine by the percentage of death for unvaccinated persons.  $Cost_F$  does not have to be added into Equation 1, since it is not affected by the amount of vaccine available, but is included here for completeness.

The variables  $R$  and  $N$  are constrained to be nonnegative.

$$R \geq 0, N \geq 0 \quad \text{Equation 2}$$

Let  $D_{nNR}$  be  $f_2 + f_3$ , the cost of all customer deaths. There are  $X_{inNR}$  customers in group  $i$ , but only  $Y_{inNR}$  of them are vaccinated, so

$$D_{nNR} = \sum_i C_i [(Q_i' Y_{inNR}) + (Q_i (X_{inNR} - Y_{inNR}))] \quad \text{Equation 4}$$

The first part of Equation 4 is the cost of the vaccinated customers. The second part of Equation 4 is the cost of the customers that were not vaccinated.

We can now write Equation 1, *TotalCost*, as the sum of those that do not seek a vaccination *Cost<sub>F</sub>*, the cost of purchasing the vaccine itself, and the cost of the customers that seek a vaccination and either receive it and still die or do not have the chance to receive it (by restrictions or shortage) and die. This is given in Equation 5.

$$TotalCost = Cost_F + R \sum_{n=0}^N P_{nN} \left[ V \left( \frac{N-n}{N} \right) + D_{nNR} \right] \quad \text{Equation 5}$$

The cost of vaccine purchased itself and the cost of the customers that do and do not receive a vaccination is calculated in the second part of Equation 5. The variables *R* and *N* should be selected to minimize this total cost.

We will consider two policies for vaccine distribution: A percentage distribution policy and a strict distribution policy. Both distribution policies use the Equations 1 through 5 above. The difference in the policies is the way that the vaccine is distributed once the number of customers is calculated. The equations below are used to determine how many vaccines there are to distribute and which customers receive them.

For the strict priority distribution policy:

$$Y_{inNR} = \min \left( X_{inNR}, R \left( \frac{N-n}{N} \right) - \sum_{j=1}^{i-1} X_{jnNR} \right) \quad \text{And } Y_{inNR} \geq 0 \quad \text{Equation 6}$$

Equation 6 reduces the vaccine available as the customers get them based on a strict priority distribution. Once all the customers in the first highest risk group based on their customer category identified in Table 3-2 are covered completely, the vaccine is then passed on to the next highest customer category that has customers not yet vaccinated. The amount of vaccine that was purchased  $R \left( \frac{N-n}{N} \right)$  is reduced during

each step by the vaccine already used for higher risk groups. The vaccination of customers continues by priority until the limit of  $R\left(\frac{N-n}{N}\right)$  number of vaccines is reached. This limit takes into account the reduction of the vaccine ordered but not purchased due to batch contamination.

Where for the percentage distribution policy:

$$Y_{inNR} = R \frac{N-n}{N} \frac{X_{inNR}}{T} \quad \text{When} \quad R \frac{N-n}{N} < T \quad \text{Equation 7}$$

$$Y_{inNR} = X_{inNR} \quad \text{When} \quad R \frac{N-n}{N} \geq T \quad \text{Equation 8}$$

The percentage of customers that receive the vaccine for each age and risk category are calculated using the percentage of the total customers in each category divided by the total number of customers in all categories. In this manner most customers in each category receive the vaccination but all the customers in each category are never completely vaccinated.

## H. RECOMMENDATIONS

Based on the fact that there is no discount for volume, the more companies that can spread the vaccination purchases is the best scenario. For the 2006-2007 influenza season the model calculated the number of vaccine doses that were required to minimize cost under the assumptions that all inactive vaccine is used appropriately for each age group, and the vaccine purchased in the United States can be divided equally into four companies. Using four companies, the purchase of 24,335,875 influenza vaccine doses provides an average death total of 44,985 and total cost of \$34.6 billion in a normal influenza season if a strict priority distribution is used as in Table 4-1, Scenario 1.

If you had enough vaccine to distribute to all who wanted a dose you could save additional lives. Utilizing the method of providing a vaccination when any member of

any population comes to purchase one the amount of vaccine needed goes up to 107,572,140 vaccine doses, which provides a death toll of 43,631 at a cost of \$35.5 billion dollars as in Table 4-2, Scenario 2.

Chances are, however, that there will not be enough time to manufacture and stockpile enough vaccine for the entire United States population. Therefore it is recommended that you aggressively target the vaccine doses to the high risk groups that will reduce overall total cost.

For example, in the best case scenario of all four companies having good batches and using the strict priority vaccination policy identified above you need only 24,335,875 vaccine doses to limit the total deaths to 10,908. If you distribute 80,679,143 doses to cover all the potential customers the death toll will drop to 9,548 deaths. This is only a reduction of 1,360 deaths with an additional 56,343,268 vaccine doses distributed and 83,236,265 additional vaccine doses purchased. This suggests that a strict priority for vaccination should be considered even during seasons where shortages have not occurred.

Based on the Vaccine Model calculations and using four companies you would order 6,083,967 doses from each of the four companies for the normal scenario utilizing the strict priority distribution policy and 52,085,151 from each of the four companies in a pandemic situation. Under the percentage distribution policy all requesting customers can be vaccinated and there is not a shortage until more than one company defaults on their shipment of vaccine.

## **I. RISK ASSESSMENT**

### **1. Cost of Life**

The argument can be made that all life no matter what age should be considered equal. Under a shortage condition, a strict priority distribution policy would be used to distribute the influenza vaccine. If the cost of life is changed and made equal for the normal influenza season with priority distribution then the total cost of the program increases to \$45.23 billion from \$34.6 billion with an additional 12 million vaccine doses required to minimize total cost. Table 3-5 outlines the cost associated with each scenario

outcome and the total expected cost of the program using the priority distribution policy. The average number of deaths would be 44,618, which are approximately 300 less than using a reduced amount for the cost of life for those 65 and older.

It will be hard politically to develop a scenario without the possibility of vaccinations provided for everyone. However, it will be impossible to try to purchase a vaccine for each individual each year based on each of the potential influenza strains that might infect the United States population.

## 2. Cost of Vaccine

The cost of vaccine on average would be \$613.58 million versus \$409.05 million for the reduced cost of all persons 65 and older. The cost of the vaccine, cost of each life lost, and the total cost of the program must be reviewed to assess the risks and costs that the country as a whole are willing to take on to adequately distribute supply of the vaccine when required. The first row in Table 3-5 corresponds to  $N=1$ , the second row corresponds to  $N=2$ , the third row corresponds to  $N=3$ , and the fourth row corresponds to  $N=4$  with each column corresponding to the number of companies  $n$  that result in contaminated vaccine batches that cannot be used.

Table 3-5. Scenario A: Normal Influenza Season Cost in Billions, Priority Distribution, and Life Cost Equal

Companies	Average Cost	all Good	1 Bad Batch	2 Bad Batches	3 Bad Batches	4 Bad Batches
1	\$ 46.47	\$ 45.22	\$ 57.69			
2	\$ 45.34	\$ 45.22	\$ 45.16	\$ 57.69		
3	\$ 45.33	\$ 45.22	\$ 45.18	\$ 49.15	\$ 57.69	
4	\$ 45.23	\$ 45.22	\$ 45.19	\$ 45.16	\$ 51.20	\$ 57.69

## J. CHAPTER SUMMARY

The Vaccine Model can identify the number of vaccine doses to be ordered during a normal influenza season and also a pandemic situation. The investment into vaccine doses that could be spread out over multiple age and risk groups was more effective when purchased. A strict priority distribution policy and a percentage distribution policy are used to determine the number of companies and the amount of vaccine to purchase from each company. The cost of the vaccine, cost of each life lost, and the total cost of the program must be reviewed to assess the risks and costs that the country as a whole are

willing to take on to purchase more than required so that an adequate supply of the vaccine is available when required. The use of the Vaccine Model provides insight into the supply and distribution of the vaccine to the customers that request it. In reviewing the model results recommendations can be made to avoid unnecessary loss of life and cost when the influenza vaccine supply does not match the required demand. In the best case scenario of all four companies having good batches and using the strict priority vaccination policy identified above you need only 24,335,875 vaccine doses to limit the total deaths to 10,908. If you distribute 80,679,143 doses to cover all the potential customers the death toll will drop to 9,548 deaths. This is only a reduction of 1,360 deaths with an additional 56,343,268 vaccine doses distributed and 83,236,265 additional vaccine doses purchased. This suggests that a strict priority for vaccination should be considered even during seasons where shortages have not occurred.

## IV. CONCLUSIONS AND RECOMMENDATIONS

### A. INTRODUCTION

A systems engineering approach to reviewing the system architecture, including the development, manufacturing, distribution, supply and demand of the influenza vaccine, was used to develop a Vaccine Model to distribute the influenza vaccine to minimize cost. Research was conducted on the manufacturing process to determine how to better manufacture the vaccine, how the vaccine was purchased, distributed to health care providers, and then provided to the public. The vaccine production and distribution system was decomposed into its separate parts to be analyzed. The production of the vaccine is difficult and there are several ways being researched to improve that portion of the system. Understanding the supply and demand chain for the influenza vaccine is helpful in developing an optimized model for ordering the correct amount of vaccine each year. (FORSBERG, 2000) The uncertainty in production amounts, the uncertainty in customer demand, and the supply and demand chain all add to the problem of getting the influenza vaccine to where it is needed each year. The architecture of the current influenza vaccine distribution system is analyzed in this thesis by utilizing the rational method (MAIER, 2002). The system characteristics were identified, the distribution system was modeled utilizing its basic elements, and the inflow and outflow requirements were identified. (HATLEY, 2002) Mathematical principles, equations, and estimated costs associated with potential deaths are utilized to develop a solution to the distribution of the influenza vaccine. Two alternative policies were developed to distribute the vaccine in the most cost effective way. The Vaccine Model was used to analyze those policies and determine the best way to distribute the vaccine to minimize cost. The development of the vaccine each year, the difficult manufacturing, the supply headaches, and the uneven demand all play into the total system that manufactures and distributes the influenza vaccine model each year.

The Vaccine Model developed in this thesis looks at the problem of how to provide for the requests each year for the influenza vaccine during each annual influenza season. Both the amount of customers requiring the vaccine or requesting it fluctuates.



The amount of vaccine to distribute to the customers each year also fluctuates due to problems relate to production. Three out of the last five years in the United States there has been some manufacturing or contamination problem affecting the amount of vaccination doses that end up for distribution to the customers in the United States. The Vaccine Model tries to identify the number of companies and the number of vaccine doses ordered per company that would be required to cover all the high-risk groups adequately if there was a problem in one or more of the companies licensed to provide the vaccine. The Vaccine Model was also used to look at a pandemic situation and determine how much vaccine should be on hand to meet the potential customer demand.

Other models in the past have included hospitalization costs to the total influenza season costs. These costs are small when compared to costs incurred with each death. The hospitalization costs associated with those that get the influenza virus could add another one billion dollars to the total cost of the influenza pandemic. The focus of this thesis is the costs associated with death each year from influenza and distribution of the influenza vaccine to minimize that cost.

## **B. KEY POINTS AND RECOMMENDATIONS**

Each influenza season is different in severity and the number of customers seeking a vaccine. A pandemic situation would add additional uncertainty to the problem. Over the past few years, however, it is clear that not enough vaccine is being produced to cover the demand. Only one out of the last four years has seen a surplus of vaccine after the conclusion of the influenza season.

Although the rational method of architecting was used to develop a solution to the stated problem, a better approach would be the participative methodology (MAIER, 2002) in which the complexities created by all the stakeholders were taken into account. The multiple stakeholders, including the companies that produce and distribute the influenza vaccine, need to agree on the overall system architecture instead of the fractured system in place today.

Four companies distributing the inactivated vaccine doses evenly could provide coverage for the population of the United States if a strict priority distribution policy is in place. Distributing the vaccine without a priority would cause the amount of the vaccine required to increase significantly.

A pandemic would require at minimum an order of around 208 million doses of vaccine spread over four companies to cover the United States population adequately if there was a 10% chance of contamination from each company. This is based on the assumption of a strict priority distribution policy. This is based on the assumption that a much higher percentage of people in each age group and category would be looking for the vaccine. If the priority distribution is not used the number of vaccines required goes up to 300 million.

The majority of the influenza seasons could be covered by purchasing fewer than 108 million doses, as in the percentage distribution policy, making sure that the doses are spread out evenly over four companies and distributed by percentage but could be reduced to as little as 24.5 million doses if necessary using a strict priority distribution policy.

Under the assumption that you can not enforce a strict priority for vaccine distribution, ordering around 26.89 million vaccine doses from four separate companies should reduce the effect of shortages in annual vaccine doses during a normal influenza season.

### **C. VACCINE MODEL RESULTS**

The number of vaccinations given to customers in Scenario 1 and Scenario 3 for the Vaccine Model is based on a strict priority distribution policy. Using four companies, the purchase of 24,335,875 influenza vaccine doses provides an average death total of 44,985 and total cost of \$34.6 billion in a normal influenza season if a strict order of vaccination is used. This is Scenario 1 and Table 4-1. The number of vaccinations given in Scenario 2 and Scenario 4 were based on percentage distribution policy. Utilizing this policy, the amount of vaccine needed in a normal influenza year goes up to 107,572,140 vaccine doses which provide a death toll of 43,631 at a cost of \$35.5 billion dollars. This is Scenario 2 and Table 4-2.

The result of not providing a large-scale immunization program based on the Vaccine Model developed would result in a cost of \$41 billion and around 58,000 deaths during a normal influenza year as shown in Tables 4-1 and 4-2 when there are no good batches to use.

Table 4-1. Scenario 1: Normal Influenza Season Cost in Billions, Priority Distribution policy, 44,985 Deaths

Companies	Average Cost	all Good	1 Bad Batch	2 Bad Batches	3 Bad Batches	4 Bad Batches
1	\$ 35.26	\$ 34.63	\$ 41.01			
2	\$ 34.72	\$ 34.63	\$ 34.80	\$ 41.01		
3	\$ 34.66	\$ 34.63	\$ 34.67	\$ 35.15	\$ 41.01	
4	\$ 34.64	\$ 34.63	\$ 34.60	\$ 34.78	\$ 36.54	\$ 41.01

Table 4-2. Scenario 2: Normal Influenza Season Cost in Billions, Percentage Distribution policy, 43,631 Deaths

Companies	Average Cost	All Good	1 Bad Batch	2 Bad Batches	3 Bad Batches	4 Bad Batches
1	\$ 36.12	\$ 35.57	\$ 41.01			
2	\$ 35.89	\$ 35.57	\$ 37.05	\$ 41.01		
3	\$ 35.69	\$ 35.57	\$ 35.73	\$ 38.37	\$ 41.01	
4	\$ 35.51	\$ 35.57	\$ 35.07	\$ 37.05	\$ 39.20	\$41.01

#### D. PANDEMIC SITUATION

If the normal influenza season turned into a pandemic situation there are several options for reducing the loss of life. One of those is not producing more inactivated vaccine. In the past during a shortage situation or a pandemic the amount of vaccine on hand was distributed to those who were thought to have the most risk of death, not by how much value they would add in the future to the economy or society. If a pandemic occurs under the current production process there would most likely be a shortage situation due to the fact that most of the population would seek out a vaccination if it was available. The pandemic influenza is modeled using a 35% attack rate. Nobody can predict the attack rate of a future pandemic but it is estimate that it would be higher than a normal influenza season (MELTZER, 1999). That scenario would double or even triple the current requests for vaccinations. The assumption used is that 80% of the population will search for a vaccination, or an estimated 225.1 million customers. A priority must be identified and followed for either shortage situation, production difficulties or a

pandemic. The distribution must also be made under the current system at least at first until other more drastic government regulations are put into place or technology progress makes the manufacturing process adaptive.

With four companies and a strict priority distribution into a pandemic situation where 80% of the population would be looking for a vaccine the amount of vaccine to be purchased would be 208,340,603 providing an average death toll of 54,798 using four companies at a cost of \$41.36 billion. This is Scenario 3 and Table 4-3. If you had all the vaccine that you needed for all the customers that wanted a vaccine you could save more lives. Using a percentage distribution policy 300,181,334 vaccine doses would be needed to cover the amount of customers that would come in for a vaccine estimated at \$225.14 million. Based on the Vaccine Model calculations and using four companies you would order 52,085,150 doses from each of the four companies in a pandemic situation using the strict priority distribution policy.

Using the percentage distribution policy in the Vaccine Model calculations and using four companies you would order 75,045,334 from each of the four companies in a pandemic situation. A total of 300,181,334 vaccine doses would need to be ordered to cover the amount of customers that would come in for a vaccine. Using four companies, there would be 53,400 deaths at a cost of \$43.01 billion dollars. This is Scenario 4 and Table 4-4.

Meltzer (1999) estimated that at a minimum the cost to the United States economy of an influenza pandemic would be around \$71 billion without a large-scale immunization. The Vaccine Model presented in this thesis estimates a cost of \$71.8 billion cost to the United States economy without an immunization program.

Table 4-3. Scenario 3: Pandemic Influenza Season Cost in Billions, Priority Distribution, 54,798 Deaths

Companies	Average Cost	All Good	1 Bad Batch	2 Bad Batches	3 Bad Batches	4 Bad Batches
1	\$ 44.39	\$ 41.35	\$ 71.77			
2	\$ 41.66	\$ 41.35	\$ 41.38	\$ 71.77		
3	\$ 41.39	\$ 41.35	\$ 41.37	\$ 41.57	\$ 71.77	
4	\$ 41.36	\$ 41.35	\$ 41.36	\$ 41.38	\$ 42.03	\$ 71.77

Table 4-4. Scenario 4: Pandemic Influenza Season Cost in Billions, Percentage Distribution, 53,400 Deaths

Companies	Average Cost	All Good	1 Bad Batch	2 Bad Batches	3 Bad Batches	4 Bad Batches
1	\$ 45.81	\$ 42.92	\$71.77			
2	\$ 44.78	\$ 42.92	\$51.60	\$ 71.77		
3	\$ 43.85	\$ 42.92	\$44.88	\$ 58.33	\$ 71.77	
4	\$ 43.01	\$ 42.92	\$41.52	\$ 51.60	\$ 62.15	\$71.77

**E. POTENTIAL AREAS TO CONDUCT FURTHER RESEARCH**

Additional studies could be done to research particular company probability rates for contamination and develop the Vaccine Model to add specific companies and contamination probabilities for a more accurate assessment. A study could be done on how the percentages would change in each age category during a pandemic. A better definition of economic loss for each age group could also be developed instead of just two categories of over 65 years old and under 65 years old. Besides the overall estimation that all categories would be increasing requests for vaccines, the question of exactly how the percentages would change for each category and what that would mean for health care providers could be researched.

**F. CHAPTER SUMMARY**

By CDC calculation, 185 million doses should be available each year to make sure an adequate supply gets to those customers who should be getting that vaccine. The Vaccine Model estimates that around 108 million on an average year are needed to minimize cost to the economy and loss of life. Each year the vaccination number produced for the influenza virus is limited and never reached 185 million. One of the distribution strategies was a strict distribution policy where the identified priority customers get the vaccine first. The other distribution strategy that was used was a percentage distribution policy that was based on distributing the vaccine as the population requested it. The percentage distribution policy is closer to a real life situation in that you usually get a percentage mix of high risk and low risk customers. If the cost of life is changed and made equal for the normal influenza season with priority distribution then the total cost of the program increases to \$45.23 billion from \$34.64 billion with an additional 12 million vaccine doses required to minimize total cost. The Vaccine Model found that four companies can adequately produce the vaccine required even if one of the

companies fails. Using the percentage distribution policy no shortage would occur unless more than one company failed to produce the requested vaccination doses. The strict distribution policy reduces the amount of vaccine doses required by under a third of that required using the percentage distribution policy in a normal influenza year.

The total cost of the vaccine program under the strict priority distribution policy would be \$34.6 billion for a normal vaccination year to \$41.36 billion for a pandemic year. Minimum cost and loss of life in a pandemic situation would be accomplished if a strict priority distribution policy was used. Under shortage conditions, the risk of not being able to cover all customers in a pandemic situation is minimized by using the strict distribution policy and a decrease in overall cost of \$1.7 billion dollars versus the percentage distribution policy with around 208 million doses ordered. The use of a strict priority distribution in a shortage situation limits loss of life to an average additional 1,300 United States citizens under a pandemic situation if the production of vaccine is spread over four companies. Actual vaccine costs are reduced by over \$1 billion dollars during a normal influenza season and over \$600 million during a pandemic year by using the strict priority distribution.

The result of not providing a large-scale immunization program based on the Vaccine Model developed would result in a cost of \$41 billion and around 58,000 deaths during a normal influenza year based on the results of the Vaccine Model. No vaccine immunization program during a pandemic would result in an economic loss of \$71.8 billion and over 100,000 deaths based on the results of the Vaccine Model.

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